3. Declaration of David P. Toman dated July 28, 1997, originally filed with Applicant's amendment mailed July 30, 1997 in serial no. 08/473,465 and with Applicant's amendment mailed Aug 1, 1997 in serial no.08/485,194.

4. Declaration of David P. Toman dated May 19, 1998, originally filed with Applicant's amendment mailed May 19, 1998 in serial no. 08/473,465.

5. Declaration of David P. Toman dated September 1, 1998, originally filed with Applicants amendment faxed September 1, 1998 in serial no. 08/485,194 and with Applicants amendment faxed September 1, 1998 in serial no. 08/473,465.

6. Declaration of Scott Leigh dated April 13, 1999, originally filed with Applicant's response faxed April 14, 1999 in serial no. 08/473,465.

35USC112, first paragraph - enablement

The appended Declarations and Attachments provide affirmative evidence that the application teaches one skilled in the art how to practice the invention as claimed without undue experimentation; specifically, how to prepare human collagen or human procollagen by recovering milk from the mammary glands of a nonhuman mammal modified to comprise an expression system encoding a human procollagen operably linked to control nucleotide sequences that effect expression specifically in milk protein-secreting epithelial cells of the mammary glands; and recovering the human procollagen or human collagen from the milk.

35USC112, second paragraph

Claims 1, 4 and 7: use of "containing" has been replaced with the equivalent, though more conventionally-used "comprising"..

Claim 1: "effect" means to cause (perhaps the word was misread as "affect"); tissue-specific expression is an art-recognized term in recombinant protein expression to distinguish non-specific, generalized protein expression. It does not preclude some "leakage" or basal expression outside the targeted tissue.

The steps of claim 1 are believed to be properly ordered: the practitioner first recovers the milk and then from the milk, recovers the recombinant protein. The expression and secretion steps are inherently performed by the recombinant mammal.

Claims 1 and 2, the use of "coding" distinguishes potential non-coding sequence which are not precluded in the expression system.

Claim 3: "the pro-α1 chain" language as been replaced with equivalent but more formal Markush language.

Claim 7: "effect" means to cause (perhaps the word was misread as "affect").

35USC103(a)

Applicants are mindful that milk has long been suggested as a convenient source material for certain small, soluble, globular proteins. What has never been suggested before is that a protein like collagen could be expressed in milk.

While many generally smaller, soluble, globular proteins have proven amenable to expression in a wide variety of systems, collagens have not. Collagens are in a league by themselves: they are enormous (hundreds of thousands molecular weight), structurally-rigid, elongated polymeric proteins which have demonstrably proven extraordinarily intractable to recombinant expression. For example, Ala-Koko et al. (1991, of record in priority applications) were only able to express a recombinant human collagen chain in conjunction with an endogenous mouse collagen in mouse 3T3 cells - i.e. a cell which is already expressing collagen. Though the structure of human collagen genes had been known for at least a decade (e.g. Barsch et al., 1991, also of record in priority applications), prior to Applicant's disclosure, no one had been able to effect targeted expression of collagen in a cell which does not normally make it (such as breast tissue).

The cited art confirm these obstacles to recombinant expression of collagen in mammalian milk. For example, Buhler et al, Krimpenfort et al, etc. only report expression of a small, globular proteins like interleukin-2 which provide none of the impediments of collagen. Khillan et al. succeeded only in systemic expression of a mini-gene version of a collagen gene.

In short, The cited art teaches that a small, globular proteins can be expressed in milk, that recombinant collagen can be expressed in a cell already making collagen, and that collagen

genes are known. These teachings do not suggest the feasibility of expressing recombinant human collagen in mammalian milk, and as such, can not suggest the claimed invention.

Double Patenting

A Terminal Disclaimer over US Patent Nos. 6,111,165, 5,895,833, 5,962,648 and 5,667,839 is enclosed.

The Examiner is invited to call the undersigned if he would like to amend the claims to clarify the foregoing or seeks further clarification of the claim language.

We petition for and authorize charging our Deposit Account No.19-0750 all necessary extensions of time. The Commissioner is authorized to charge any fees or credit any overcharges relating to this communication to our Dep. Acct. No.19-0750 (order C94-007-1-D4).

Respectfully submitted,
SCIENCE & TECHNOLOGY LAW GROUP

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Encl. "To Help Our Customers Get Patents"
Mission Statement, USPTO External Customer Services Guide

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7. Terminal Disclaimer.

VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (Amended) A method to prepare human collagen or human procollagen, which method comprises:

recovering milk from the mammary glands of a nonhuman mammal which mammal has been modified to [contain] comprise an expression system which comprises a coding nucleotide sequence encoding at least one human procollagen operably linked to control nucleotide sequences that effect expression specifically in milk protein-secreting epithelial cells of said mammary glands under conditions wherein said coding nucleotide sequence is expressed to secrete human procollagen or human collagen into the milk of said mammal; and

recovering the human procollagen or human collagen from the milk.

2. (Unamended) An expression system for production of human procollagen or human collagen in milk which expression system comprises a coding nucleotide sequence encoding human procollagen operably linked to a promoter capable of specifically effecting expression in milk protein-secreting cells of mammary glands.

3. (Amended) The expression system of claim 2 wherein the human procollagen [is the] comprises a procollagen chain selected from the group consisting of a pro-α1 chain of type I collagen or [is the] a pro-α1 chain of type III collagen.

4. (Amended) A fertilized nonhuman egg [containing] comprising the expression system of claim 2.

5. (Amended) A nonhuman embryonic stem cell modified to [contain] comprise the expression system of claim 2.

6. (Unamended) A transgenic nonhuman mammal which comprises the expression system of claim 2.

7. (Amended) The nonhuman mammal of claim 6 which has been further modified to [contain] comprise at least one expression system which effects the production of post-translational modification enzymes for procollagen.